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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/687,576	10/16/2003	Samuel F. Hunter	11918N/021452	7769

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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 02/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/687,576	HUNTER, SAMUEL F.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-33* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/21/04, 6/18/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1 – 33, each in part, drawn to methods for treating diseases comprising administering compositions, wherein the delivery is oral or parenteral, classified in class 514, subclass 12, for example.

   II. Claims 1 – 33, each in part, drawn to methods for treating diseases comprising expressing transfected genetic material in vivo, classified in class 514, subclass 44.

2. The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions require different starting materials. Invention I can be performed with protein, for example, whereas invention II requires nucleic acid. Nucleic acids are patentably distinct from proteins as the molecules have different physical and biochemical properties. Furthermore search for methods of treating disease by expressing genetic material will not be informative as to the novelty of methods of parenteral or oral administration of a protein. Thus consideration of Groups I and II together would be burdensome for the examiner.

3. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter and because they require different searches, restriction for examination purposes as indicated is proper.

4. During a telephone conversation with Richard Myers on 9 February 2006 a provisional election was made without traverse to prosecute the invention of Group I, claims 1 – 33, to the extent that they are drawn to oral or parenteral administration. Performing the method by expression of transfected nucleic acid in vivo will not be searched or considered. Affirmation of this election must be made by applicant in replying to this Office action.

Claim Objections

5. Claims 3, 17, 25, and 30 are objected to because of the following informalities: they recite non-elected subject matter, specifically "expression of transfected genetic material in vivo". Appropriate correction is required.

6. Claims 2 and 16 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims are drawn to ligands which are either natural, recombinant, or synthesized, but this does not limit the base claims as the ligands could not conceivably anything other than natural, recombinant, or synthesized.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 – 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administration of compositions comprising granulocyte-macrophage colony stimulating factor, does not reasonably provide enablement for administration of a "colony stimulating factor-like ligand," or for treatment of any disease or condition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

In the instant case, the nature of the invention, that is, treatment of demyelinating diseases by administering cytokines, is complex. This involves the interaction between the

central nervous system, the locus of disease, and the immune system. As both of these systems are themselves complex and comprised of many interacting sub-parts, the interface between them is quite complex indeed. The claims encompass treatment of either demyleinating diseases in general (see, for example, claim 1) or multiple sclerosis (MS) in particular (see claim 15, for example).

The specification provides a single working example, beginning on page 13, describes the results of experiments in which GM-CSF was administered to patients with MS. The specification discloses that patients were treated simultaneously with interferon-beta-1a and sargramostim (see p. 13); sargramostim is synonymous with GM-CSF (see attached printout from NCI terminology browser) and that such treatment resulted in improvement on the EDSS and MSFC scales (see p. 13, and Figures 1 and 2). However the data presented are not sufficient to enable treatment of MS by administration of GM-CSF. There is no indication as to whether the changes observed are statistically significant, and given the large size of the error bars, particularly in Figure 1, it appears that the changes over time are so small with respect to the variability that such changes would be expected by random variation alone. Additionally, the data presented include no control group. Interferon was well-known in the prior art to be an effective treatment of multiple sclerosis (see Polman et al. (2000) British Medical Journal 321:490-494, particularly the paragraph spanning pp. 491 – 492). Since no control group was used, it is impossible to tell the improvements seen are any different from those seen after administration of interferon alone. It is simply impossible to tell whether the improvement in the two MS disease scales is better, worse, or no different after administration of GM-CSF and interferon compared to interferon alone.

Additionally, there is considerable scientific reason to doubt the efficacy of GM-CSF in the treatment of multiple sclerosis. McQualter et al. (2001. Journal of Experimental Medicine 194:873-881, cited by applicant on IDS filed 18 June 2004) teach that mice that lack GM-CSF do not develop experimental autoimmune encephalomyelitis (EAE, an art-accepted mouse model of MS) upon immunization with myelin oligodendrocyte protein (MOG). However, when recombinant GM-CSF is given to mice lacking endogenous GM-CSF, they do in fact develop EAE after administration of MOG. Similarly, wild-type mice given MOG develop EAE to the same extent whether they are given GM-CSF or not (see McQualter et al. Figures 1 and 2). Clearly the presence of GM-CSF exacerbates the course of demyelinating disease in those mice that lack the protein, and appears also exacerbate the course of EAE in wild-type mice.

Additionally, McQuarter teaches that treatment of wild-type mice with antibodies against GM-CSF delays the onset and attenuates the severity of symptoms of EAE when the antibodies are administered when the disease is induced, and in fact ameliorates the symptoms of EAE when the antibodies are administered after the onset of symptoms.

Openshaw et al. (2000. Neurology 54:2147-2150, cited by applicant on IDS filed 18 June 2004) teaches that administration of GM-CSF to human patients exacerbates the symptoms of multiple sclerosis. Openshaw furthermore teaches that GM-CSF in general exacerbates immune-related conditions (see p. 2149, first column) and as MS is well-known to have an autoimmune component, a worsening of symptoms upon administration of any dose of the compound would be expected not to be therapeutically effective, but rather to be deleterious.

Thus the prior art clearly indicates that GM-CSF is not a therapeutically effective treatment of demyelinating disease, but rather that it exacerbates disease. Since the data in the sole working example in the specification are confounded by the lack of a control group, it is improper to conclude that they teach the artisan how to treat a disease by administering GM-CSF. As all pending claims require administering a therapeutically active amount of a CSF or a CSF-like ligand, and GM-CSF is not therapeutic, it would not be possible for a skilled artisan to determine the dose required. Thus undue experimentation would be required in order to make and use the invention commensurate in scope with the claims.

Additionally, the specification is not enabling for the full scope of "colony stimulating factor-like ligand". This is a very broad term and has no structural limitation. There is no requirement that the ligand have any particular shape, size, or charge, only that in some way it be "like" a CSF ligand. The only working example in the specification is drawn to administration of GM-CSF. There is no disclosure of administration of any CSF-like ligands, nor is there disclosure of what such a ligand even is. Thus given the breadth of the claims which either recite this limitation or depend from such claims (i.e. all pending claims), and the fact that the specification discloses no members that fall within genus other than GM-CSF, which is not *like* a CSF ligand but in fact *is* a CSF ligand, it would take undue experimentation in order for a skilled artisan to make and use the invention commensurate in scope with the claims.

8. Claims 1 – 33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claimed invention encompasses "colony stimulating factor-like ligands" used in methods of treating diseases. The specification does not describe any such ligands. Thus in the absence of describing these ligands, one skilled in the art could not conclude that the inventor had performed the claimed method by administering the compounds. Furthermore the specification does not disclose the treatment of a genus of demyelinating diseases (as it relates to claims 1 – 12, and 14 but only describes the results of experiments in which patients with MS were given GM-CSF. Thus there is not adequate written description of treatment of demyelinating diseases in general by administering therapeutically effective amounts of the recited agents.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 – 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, from which all other claims depend, as well as claims 2 – 5, 7, 11, 16 – 19, 22, 24 – 27, 29 – 32, all recite the term "...stimulating factor-like ligand". The term "...stimulating factor-like ligand" in claims 1 – 5, 7, 11, 16 – 19, 22, 24 – 27, 29 - 32 is a relative term which renders the claim indefinite. The term "...stimulating factor-like ligand " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not possible to tell what ligands are "like" CSF ligands.

Claim 4 recites the limitation "therapeutically effective means including transmucosal...". This recitation is akin to an improper Marksuh group. Proper Markush groups use the phrasing "selected from the group consisting of" not "selected from the group comprising". Alternative limitations in claims are acceptable, so long as the inclusion of them does not render the scope of the claim indefinite. See MPEP § 2173.05(h). In the instant case, it is not possible to determine the metes and bounds of claim 4 because a skilled artisan could not determine which "therapeutically effective means" fall outside the scope of the claim.

Claims 12, 23, 28, and 33 are indefinite because they depend from claims 1 and 29 respectively, which are both method claims, however these dependent claims only recite additional products and not steps. A method cannot comprise a compound alone, it must comprise active steps.

Claims 7, 19, 27, and 32 are indefinite because they recite "wherein said colony stimulating like-factor is sargramostim". However sargramostim is not like a factor that is like a CSF; it is a factor that is a CSF. In fact, it is synonymous with GM-CSF. Thus these claims are indefinite.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 – 6, 13 –18, 24 – 26, and 29 – 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Von Feldt (U.S. Patent 5,837,460, issued 17 November 1998).

Von Feldt teaches administration of GM-CSF antagonists for treatment of many inflammatory diseases, including multiple sclerosis. See column 9 lines 39 – 55. The claims encompassed by this rejection do not require that the "colony stimulating factor-like ligand" have any particular activity, either agonistic or antagonistic. The claims only require administration of therapeutically effective amount of CSF-like ligands. As Von Feldt teaches administration of peptides which mimic GM-CSF, the prior art reference anticipates claims 1, 13, 15, 24, and 29. The compounds taught by Von Feldt are synthetic (see column 9 lines 19-20) meeting the limitations of claims 2 and 16. The reference also teaches intravenous, subcutaneous, and intramuscular administration, as it relates to claims 3 – 4, 17, 25, and 30 (see column 10 lines 6 – 14). As claims 5, 6, 18, 26, and 31 only require that the GM-CSF be "biologically active", and the ligands of Von Feldt are active in that they are GM-CSF antagonists, the reference also meets the limitations of these claims. Note that claim 6, which depends from claim 5, is limited to biologically active molecules, which implies that claims 18, 26, and 31 include such biologically active molecules as well. Claim 14 recites all forms of MS, and thus even though

these forms are not explicitly listed in the Von Feldt reference, the skilled artisan would know that it inherently includes all forms of MS.

11. Claims 1 – 4, 12 – 17, 23 – 25, 28 – 30, and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee (U.S. Patent 6,187,756, issued 13 February 2001).

Lee teaches methods of treating neurological conditions, including MS (see column 5 lines 16 – 21 and claims 1 and 8). The methods are to be performed by administering immunomodulators, including colony stimulating factors (see column 19 lines 33 – 45 from Lee) and Lee also teaches how to determine a therapeutically effective amount (see column 16 lines 5 – 26). Thus the reference teaches all elements of claims 1, 13 – 15, 24, and 29. Claims 2 and 16 are drawn to agents which are natural, recombinant, or chemically synthesized, but since this does not further limit the agents of claims 1 and 15 respectively, the reference necessarily anticipates these claims as well. The reference teaches multiple modes of administration including injections (subcutaneous and intramuscular; see column 17 lines 12 – 15), as well as transdermal (i.e. transcutaneous; see column 17 line 65) and thus meets the limitations of claims 3 – 4, 17, 25, and 30. The reference also teaches that colony stimulating factors are immunomodulators (see column 19 lines 33 – 45 and claims 2 and 12) and thus meets the limitations of claims 12, 23, 28 and 33.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 – 6, 8 – 10, 12 – 18, 20 – 21, 23 – 26, 28 – 31, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Von Feldt (U.S. 5,837,460), Lee (U.S. 6,187,756) and, Polman et al. (2000) British Medical Journal 321:490-494.

The reasons why the Von Feldt and Lee references anticipate claims 1 – 6, 13 – 18, 24 – 26, and 29 – 31 and claims 1 – 4, 12 – 17, 23 – 25, 28 – 30, and 33 respectively are set forth in the rejections under 35 USC § 102(b) above. Briefly both references teach methods of treating multiple sclerosis by administration of colony stimulating factor-like ligands and colony

stimulating factors. However neither Von Feldt nor Lee teaches administration of interferon beta 1a, as it relates to claims 8 – 10 and 20 – 21.

Polman teaches administration of interferon beta 1a for treatment of multiple sclerosis (see paragraph spanning pp. 491 – 492). However Polman does not teach administration of colony stimulating factor-like ligands and colony stimulating factors.

It would have been obvious to one of ordinary skill in the art to co-administer the interferon beta 1a (as taught by Polman) with either of the compositions taught by Von Feldt or Lee. The motivation to co-administer them would be to more effectively treat multiple sclerosis. See MPEP 2144.06, "Combining equivalents known for the same purpose". Here, all compounds were known to be effective for treatment of multiple sclerosis.

Conclusion

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DK

Daniel E. Kolker, Ph.D.
February 16, 2006

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Primary PATENT EXAMINER